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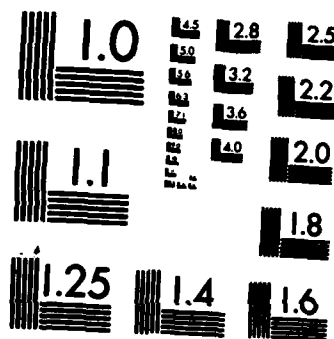
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EVALUATION OF L-TRYPTOPHAN FOR TREATMENT OF INSOMNIA: A REVIEW

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EVALUATION OF L-TRYPTOPHAN FOR TREATMENT
OF INSOMNIA: A REVIEW¹

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To expedite communication of our research, this is a preprint of a paper submitted to Psychopharmacology and should be cited as a personal communication.

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²Director, Research Department, Psychiatric Clinic, Koenigsfelden, Switzerland, on sabbatical leave at the Naval Health Research Center when this manuscript was prepared.

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SUMMARY

Sleep laboratory and outpatient studies of the hypnotic efficacy of the amino acid l-tryptophan are reviewed, with particular emphasis on evaluation of therapeutic effectiveness in the treatment of insomnia. In younger subjects, for whom insomnia is a situational disturbance and whose sleep problem consists solely of longer than usual sleep latencies, l-tryptophan is effective in reducing sleep onset time on the first night of administration in doses ranging from 1-15 grams. In more chronic, well-established sleep onset insomnia or in more severe insomnias characterized by both sleep onset and sleep maintenance problems, repeated administration of low doses of l-tryptophan over time may be required for therapeutic improvement. In these patients, hypnotic effects appear late in the treatment period or, as shown in some studies, even after discontinuation of treatment. The improvement in sleep measures posttreatment has given rise to use of a treatment regimen known as "interval therapy", in which l-tryptophan treatment alternates with an l-tryptophan-free interval until improvement occurs. The absence of side effects and lack of development of tolerance in long-term use are important factors in the decision to embark upon a trial of l-tryptophan treatment. In addition, l-tryptophan administration is not associated with impairment of visuomotor, cognitive, or memory performance nor does it elevate threshold for arousal from sleep.



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INTRODUCTION

Evaluation of the hypnotic efficacy of the amino acid l-tryptophan is based on the fact that l-tryptophan is an essential dietary constituent and the precursor of serotonin, a transmitter which has been shown in some neurophysiological studies to be involved in sleep-wake mechanisms. Use of a physiological agent suspected to have a direct relationship with sleep regulation and for which natural metabolic pathways are present suggests that treatment of insomnia may be offered without production of undesirable side effects and risks of toxicity.

Despite the accumulation of substantial knowledge on neurophysiological regulation of waking and sleep, specific predictions have not been advanced as to the pathophysiology of various types of insomnia which could be explicitly tested. Studies with l-tryptophan, conducted as early as 1966 (Oswald et al. 1966), have therefore been empirical in nature. Two reviewers (Hartmann 1977; Cooper 1979) agreed on the safety of l-tryptophan intake and its sleep-inducing effects but did not make a positive recommendation for the clinical use of tryptophan as a sleeping aid. Hartmann (1977) pointed out that "further work is needed to establish whether l-tryptophan would be effective in more serious insomnia and to compare its efficacy with that of established hypnotic agents". Cooper (1979) came to the conclusion "that tryptophan administered at night in dosage between 1 gram to 15 grams has some sedative properties, but the optimal dose and the precise profile of this action, and whether or not it has clinical utility, remains to be determined". The Institute of Medicine Report (1979) on sleeping pills also raised these same issues. More recent studies have contributed to the evaluation of the clinical usefulness of l-tryptophan. Therefore, it is of value to reexamine the earlier studies in light of recent findings with particular attention focused on the effectiveness of l-tryptophan in the management of insomnia.

Effects of L-Tryptophan on Sleep Onset

In a number of studies using subjects with long sleep latencies, the hypnotic efficacy of l-tryptophan in inducing more rapid sleep onset was assessed over a wide dose range. Hartmann et al. (1974) gave 1, 2, 3, 4, 5, 10 and 15 grams, each once, to subjects 21 to 35 years of age. They found that sleep onset latencies were reduced from a placebo mean of 24.2 minutes to means ranging from 10.8 to 16.1 minutes after l-tryptophan. Reductions in sleep latency were statistically significant at all doses except the 2 gram dose. Experiment 2 of Griffiths et al. (1972) also demonstrated the hypnotic effect of high doses: 12 grams, given 30-60 minutes before bedtime to young adults, significantly reduced sleep latency from 31.3 minutes to 18.5 minutes. However, in these subjects, the frequency of brief arousals during the night was increased, indicating that this high dose might not be appropriate for the treatment of insomnia. In the low dose range, the efficacy of 1 gram was later confirmed by Hartmann and Spinweber (1979), but smaller doses - 0.5 gram and 0.25 gram - did not significantly reduce sleep latency. Hartmann and Elion (1977) tested the effect of a single administration of 1 gram and 3 grams l-tryptophan compared to placebo on the situational sleep disturbance that is sometimes encountered when a person sleeps in the sleep laboratory for the first time - the so-called "first night effect". Both doses significantly shortened sleep latency. Brown et al. (1979) studied acute treatment with 1 gram and 3 grams l-tryptophan in females who had problems falling asleep. The 1 gram dose was administered only once and had no effect. The 3 gram dose was given on three occasions separated by one month intervals and on three successive nights in the final trial. Sleep latency was reduced in the first study week only. However, the sleep latency measures decreased steadily across the study in those subjects with very long initial latencies. A regression analysis showed that sleep latency was significantly shorter on l-tryptophan nights as compared with placebo nights. In another study, Adam and Oswald (1979) tested 1 gram l-tryptophan in 12 older subjects (age range 38-65 years), whose sleep latencies varied greatly, and in whom the progression of sleep onset was very slow, with prolonged stage 1 mean latency of 18.4 minutes and stage 2 latency of 47.8 minutes. These latencies remained unchanged with l-tryptophan treatment.

The results of these studies indicate that l-tryptophan reduces the time required for sleep onset, when the subject's baseline latencies are longer than normal. L-tryptophan is most likely to be effective on the first night of administration in younger subjects whose sleep onset insomnia is situational and not chronic in nature. Depending on the subject's initial condition, sleep latency may be significantly reduced with doses ranging from 1 gram to 15 grams. For low dosages, especially, it seems important that they are given at least some 30-45 minutes before bedtime to allow absorption of a significant amount of l-tryptophan, which reaches peak plasma concentration one to two hours after ingestion (Domino 1976; Yuwiler et al. 1981). The smallest effective dose is 1 gram in acute treatment. There is no clear dose-response relationship up to 10 grams. As previously discussed by Spinweber et al. (1983), in situations not conducive to sleep and/or in subjects with short sleep latencies, l-tryptophan does not significantly reduce sleep onset time (Griffiths et al. 1972; Nicholson and Stone 1979; Small et al. 1979; Wyatt et al. 1970).

Hypnotic Effects of L-Tryptophan in Severe Insomnias

The studies discussed in this section evaluated l-tryptophan in subjects characterized by various types of persistent insomnias. Most subjects in this category were middle-aged people presenting as insomniac patients without major psychiatric or medical problems, although some studies included younger chronic insomniacs as well. Wyatt et al. (1970) first administered 7.5 grams l-tryptophan for ten consecutive nights to five young females and recorded ad lib sleep. There was a significant ($p < 0.01$) large increase in total sleep time during treatment, with mean total sleep increasing from 473 minutes to 541 minutes. In Wyatt's second experiment, 7.5 grams l-tryptophan were administered over a period of 5-10 consecutive nights to seven older patients (age range 48-68 years) with both sleep onset and maintenance problems, including early morning awakenings. There were significant improvements in mean total sleep time (+72 minutes), amount of intermittent awakenings (-27 minutes), and early morning wakefulness (-36 minutes), but no significant change in sleep latency.

One patient in the Wyatt et al. (1970) study showed a dramatic increase of total sleep time from 169 minutes on pretreatment placebo to 262 minutes on posttreatment placebo. This subject's total sleep time posttreatment was actually the same as that during treatment with l-tryptophan (257 minutes), and the improvement was due primarily to a sustained reduction of sleep latency and decreased early morning wakefulness. Inspection of this subject's data raised the question of whether repeated administration of l-tryptophan produced a build-up of hypnotic effects or a persistent effect after discontinuation. Gnirss et al. (1978) administered 2 grams l-tryptophan twice in a completely randomized order over four successive nights to severe insomniacs. A beta-blocker, Oxprenolol, was also administered; however, since further investigation in the same laboratory indicated that it was unlikely that Oxprenolol had any influence on the action of l-tryptophan, this study, as well as others which used this combination of agents, are included in this review. Gnirss et al. (1978) found no difference in insomniac sleep characteristics between the l-tryptophan and placebo nights. However, a post hoc analysis which involved regrouping the nights according to the sequence of treatment revealed sequential treatment effects on sleep latency and total sleep time, both of which improved on the placebo nights that followed l-tryptophan administration compared to pretreatment placebo nights. It is interesting that this phenomenon was previously reported by Hartmann et al. (1971) who also grouped the placebo nights according to their sequence in a post hoc analysis and found the greatest improvement on the posttreatment placebo night. Since the effect did not reach statistical significance, the authors interpreted it to be "slight sequential improvement". Nedopil and Brandl (1980) administered 1 gram l-tryptophan and 80 milligrams Oxprenolol over three nights of telemetrically-recorded home sleep. They first found a worsening effect during early administration of this combination on sleep latency and total sleep duration. Sleep then improved on the third night, and this beneficial effect persisted on the two posttreatment placebo nights.

Spinweber and Johnson (1983) recently reported a build-up of the sleep latency reducing effects of 3 grams l-tryptophan administered to young poor sleepers over six consecutive nights. The reduction in sleep latency both within the treatment group and compared to a placebo group reached statistical significance only in the second half of the 6-night treatment period. Moldofsky and Lue (1980) investigated early and late effects (treatment nights 1-4 and 17-18) of 5 grams l-tryptophan given every night to insomniac 'fibrositis' patients. In comparison to pretreatment placebo, there were no significant changes in the early treatment period; however, during late treatment, a significantly shorter sleep latency and decreased stage 1 were recorded.

Gnirss et al. (1980) also described the presence of hypnotic after-effects in a longitudinal case study. Based on such results, Schneider-Helmert (1981) studied severe chronic insomniacs to evaluate this effect. L-tryptophan 2 grams was given on three successive nights. The period of four posttreatment placebo nights was then compared with the four baseline placebo nights. For testing the hypothesis of a sleep improvement by l-tryptophan on the postdrug interval, a predictive procedure was used. The result was statistically significant at the preset level for rejecting the null hypothesis. Post hoc analysis of variance of the group values showed highly significant improvements in the postdrug period as compared to baseline in the measures of sleep latency, total wake time, and arousal density, and mean total sleep duration was increased by one hour.

In summary, these sleep laboratory studies have confirmed the efficacy of l-tryptophan treatment in chronic insomnias. As discussed earlier, in younger sleep onset insomniacs, a therapeutic effect has been demonstrated with a single administration of l-tryptophan at doses as low as 1 gram. Severe chronic insomniacs, on the other hand, seem to require repeated administration until sleep improvement occurs. In this population, the therapeutic effect encompasses changes in multiple sleep variables and is not limited to decreases in sleep latency. It has also been shown that hypnotic effects may persist following discontinuation of short-term administration of l-tryptophan for several nights.

Clinical Studies in Insomniac Out-Patients

In addition to sleep laboratory studies, there have been evaluations of effects in insomniac outpatients in which the dependent measures are subjective reports. Hartmann et al. (1983) compared a group of 29 patients treated for one week with 1 gram l-tryptophan, followed by one week on placebo, with a placebo group. The subjects were drawn from 95 middle-aged chronic insomniacs who presented for treatment at a primary care clinic. Data on sleep were obtained from a postsleep questionnaire. There was no difference between the l-tryptophan and placebo groups. However, within the l-tryptophan group, sleep latency in the posttreatment week was significantly shorter than in the treatment week, suggesting a replication of the sequential effect. This effect was built up during the late part of the treatment week, according to the presented graph. According to subgroup comparisons, the insomnia type complaining of several discrete awakenings during the night responded with especially good global outcome. These results support some of the findings of laboratory studies, such as interval effects (Schneider-Helmert 1981) and build-up of effects on sleep latency (Spinweber and Johnson 1983), but the weakness of the effect in the Hartmann et al. (1983) study suggests that 1 gram may be the lowest and only a marginally effective dose for short-term treatment of chronic insomnia.

The marginal efficacy of the 1 gram dose may, however, be more marked in longer-term treatment. Steinberg et al. (1981) reported the results of a study on twenty middle-aged chronic insomniacs who were treated with 1-2 grams l-tryptophan (plus 80 milligrams Oxprenolol) for one to four months of continuous administration. Six of the patients were followed for four months. Self-reported total sleep duration increased steadily from the second week through the second month of treatment from a pretreatment mean of 2.9 hours to 5-6 hours of sleep per night. This value was still below that of an age and sex-matched control group of good sleepers, but the increase in the amount of reported sleep was correlated with an improvement of perceived sleep quality from 'medium to bad' to 'good to

medium' at the end. The improvement in reported sleep time and quality were maintained by the six patients during the follow-up period. The fact that the first nights on l-tryptophan were not altered compared to pretreatment may be considered to be an indication that there is a delayed action of l-tryptophan. It also rules out a possible placebo effect of l-tryptophan administration. Another finding - that the desired sleep duration of the patient group was the same as that of the control group - supports the reliability of subjective estimates in such patients with chronic, severe insomnia.

Schneider-Helmert (1982) and Schneider-Helmert and Bodmer (1983) reported the outcome of long-term 'interval therapy' in forty middle-aged chronic insomniacs who were treated by seven different physicians. The treatment consisted of repeated cycles of three nights on l-tryptophan (2 grams) followed by a four-night interval off l-tryptophan. Repeated assessments of sleep quality were obtained from physicians using standardized rating forms which were completed following consultation with their patients. Outcome was considered positive if reduction of insomniac symptoms was complete or if improvement was such that further treatment was neither desired by the patient nor considered necessary by the physician. After the termination of the long-term treatment, which lasted on average four to five months, 80 percent of the patients had positive outcomes. Two-thirds of the patients who had previously been treated unsuccessfully with sedative hypnotics had nearly the same percent of positive outcomes as those initially treated with l-tryptophan. This finding mitigates against the notion that the results of the l-tryptophan treatment were merely a placebo effect. Twenty patients were followed for 6 months to 2 years after termination of the long-term interval therapy with l-tryptophan. They showed a definitive 90 percent success rate.

These studies of l-tryptophan suggest that severe chronic insomniacs respond especially well to long-term, low-dose treatments. There was usually a delay in treatment effects, though. Reports of late-appearing hypnotic effects are consistent with laboratory findings. Three sets of findings indicate that l-tryptophan may be employed on a long-term basis as an effective therapeutic aid by severe chronic insomniacs: (1) the absence of side effects; (2) the lack of tolerance, as evidenced by the time course of symptom reduction, which progressed rather than faded over time of treatment; (3) the good results of follow-up studies indicating l-tryptophan might lead to a definitive recovery from insomnia. These studies also suggest that "interval therapy" may be an especially effective treatment strategy for use in chronic insomnias.

Insomnias Associated with Other Conditions

Hartmann (1970) and Hartmann et al. (1971) reported the results of a study on 24 insomniac schizophrenic inpatients who were given single doses of 2, 3, 4, and 5 grams l-tryptophan on separate occasions. Sleep was assessed by behavioral observations every 15 minutes and by morning interviews and questionnaires. In the whole group, only the 5 gram dose improved sleep latency and total sleep duration significantly. In a subgroup of 14 patients, who slept less than seven and a half hours, these improvements were also found with 4 grams l-tryptophan. The authors pointed out that only rough time estimates can be given in a study relying on discontinuous observations; increase of total sleep duration was thus approximately three quarters of an hour with 5 grams l-tryptophan. Subjective evaluation of sleep quality and morning mood were significantly better after l-tryptophan nights. No side effects and no change of blood pressure 9 hours after administration of l-tryptophan were seen.

Linnoila et al. (1980) administered 3 grams l-tryptophan for seven nights to 19 female psychogeriatric inpatients, mean age of 77.4 years. Sleep was assessed by nurse ratings every fifteen minutes. No change was found in latency or total duration of sleep, either during treatment or in three nights thereafter. The absence of any side effects on memory, orientation, or motor performance in the mornings after the last treatment with l-tryptophan is noteworthy in this group of highly sensitive patients.

A study by Brezinova et al. (1972) addressed the problem of whether 7.5 grams l-tryptophan would suppress the occurrence of withdrawal insomnia in chronic users of barbiturates, glutethimide, or benzodiazepines, which would imply that l-tryptophan served as a pharmacological substitution of those sedative hypnotics. No hypnotic effects were present in this group.

DISCUSSION

This review of studies on the hypnotic efficacy of l-tryptophan indicates the following pharmacological features of its use:

(1) The lowest effective dose of l-tryptophan in acute treatment is 1 gram. Within the range from 1 to 10 grams, i.e., a ten-fold increase in dosage, there is no clear dose-response relationship. It appears that the minimum effective dose may vary depending upon the severity of the insomnia. Therefore, to obtain reliable effects on sleep latency in acute treatment, l-tryptophan should be administered at least 30 to 45 minutes before bedtime at a dose between 1 gram and 5 grams, depending on the degree of sleep disturbance.

(2) Chronic insomniacs appear to respond to low doses of l-tryptophan only after repeated administration. Perhaps the disturbed regulatory system of the chronic insomniac is too rigid to react immediately to a therapeutic increase of a natural agent.

(3) Short-term repeated administration of l-tryptophan may result in a sequential improvement, i.e., therapeutic effects on sleep occurring during the l-tryptophan-free interval. Four different studies found the interval effect with total doses of 3-6 grams for 3-6 days (Gnirss et al. 1978; Hartmann et al. 1983; Medopil and Brandl 1980; Schneider-Helmert 1981). It could be speculated that delayed effects occurring during continued l-tryptophan administration of Spinweber and Johnson (1983) and Steinberg et al. (1981) were masked interval effects, since they occurred after a similar total dose and time period. The basis of the sequential effect is not yet understood. Schneider-Helmert and Bodmer (1983) speculated that homeostatic regulation might reduce the passage of l-tryptophan into the CNS and/or reduce the sensitivity of serotonergic cells with continuous administration of tryptophan and that these mechanisms may be by-passed during the l-tryptophan-free interval. All studies reporting some kind of interval effect were done with chronic insomniacs. This subject factor may indicate that the interval effect is the result of a specific interaction between treatment and disorder rather than a pure pharmacological feature of l-tryptophan administration.

Recent evaluations of outcome and follow-up after long-term treatment with l-tryptophan are exceptionally positive. Two studies (Steinberg et al. 1981; Schneider-Helmert 1982) investigated chronic primary insomniacs, patients who are known to be rather difficult to treat. It is not possible, at this time, to determine whether there is a difference in efficacy between a prolonged trial of continuous administration and the interval mode. However, as Schneider-Helmert (1982) pointed out, interval therapy has the additional advantage of preventing the development of psychological dependence with consistent nightly use.

(4) The lack of side effects, even with high doses, in administration over long periods of time, or in especially sensitive populations, is of great practical value. The absence of side effects is certainly explained by the fact that absorption as well as metabolism of l-tryptophan proceed according to physiological mechanisms that are established and in continuous action for that very purpose.

(5) No indications of the development of tolerance under continuous long-term administration were found. In the range of therapeutic doses, l-tryptophan did not affect the normal distribution of sleep stages, neither in acute treatment (Griffiths et al. 1972; Hartmann 1967; Hartmann et al. 1974; Hartmann and Spinweber 1979; Nicholson and Stone 1979; Oswald et al. 1966) nor chronic treatment (Hartmann and Cravens 1975).

(6) The efficacy of l-tryptophan in insomnias associated with other conditions appears questionable. Certainly, this point needs further exploration.

Sedation, i.e., direct CNS depression, is the main component of the actions of sedative hypnotics. However, besides increasing sleep, sedation has consequences which are not a component of natural sleep, such as impaired psychomotor and mental performance, which could be harmful to the patient in particular situations. Because l-tryptophan is a physiological agent, it is possible that it has a more direct influence on sleep regulation without requiring CNS depression for this action. Studies on the effects of l-tryptophan on the waking EEG either showed no effect with 5 grams (Oswald et al. 1966) or a shift toward more theta or alpha activity (Greenwood et al. 1974; Spinweber 1981) with a high dose injected intravenously or with 4 grams orally, respectively. In the Greenwood et al. (1974) study, the spontaneous behavior of the subjects and the results of performance tests, which showed only minor decrements at high doses, are consistent with the absence of adverse effects of 2 grams on psychomotor performance (Broadhurst 1977). Increased reported sleepiness was found with doses of 1 gram to 4 grams (Hartmann et al. 1979; Hartmann et al. 1983), demonstrating that l-tryptophan induced relaxation rather than sedation. Spinweber and Johnson (1983) found no effect of 3 grams l-tryptophan administered 45 minutes before bedtime on auditory arousal thresholds, memory, or performance in various tests during the night as well as on the following morning. It is evident, thus, that l-tryptophan has no primary sedative effects.

The fact that l-tryptophan is a nonsedative hypnotic gives some indications as to its mode of action and thus of its advantages and limitations. At sleep onset, it seems to facilitate a preparatory relaxation, but since no important sedation is induced, the problems of nighttime or 'hangover' sedation, otherwise related to the pharmacological treatment of insomnia, are avoided. Therefore, l-tryptophan has a special indication in patients who may be required to awaken and perform certain tasks during the time course of action of the hypnotic. On the other hand, sedation may be specifically desirable in cases where insomnia is a secondary symptom of neurotic or psychotic agitation. Though this special problem has not yet been investigated, it seems unlikely that the sleep regulating properties of l-tryptophan would overcome the basic disturbance. Bridges et al. (1976) found the ventricular CSF l-tryptophan levels significantly higher in agitated compared to nonagitated psychiatric patients, so there is no physiological justification for increasing l-tryptophan in the central nervous system of such patients. Accordingly, two clinical studies in depressive patients reported that agitation and anxiety were not significantly reduced by l-tryptophan (Herrington et al. 1976; Lindberg et al. 1979).

Based on the reviewed studies, it appears that l-tryptophan has significant hypnotic efficacy in the treatment of acute and, even more so, chronic primary insomnias in all instances except those requiring primary sedation. More clinical studies are needed to clarify the differential indications and to determine which populations may benefit from l-tryptophan treatment with a definitive recovery.

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well-established sleep onset insomnia or in more severe insomnias characterized by both sleep onset and sleep maintenance problems, repeated administration of low doses of l-tryptophan over time may be requisite for therapeutic improvement to occur. In these patients, hypnotic effects appear late in the treatment period or, as shown in some studies, even after discontinuation of treatment. The improvement in sleep measures posttreatment has given rise to use of a treatment regimen known as "interval therapy", in which l-tryptophan treatment alternates with an l-tryptophan-free interval until improvement occurs. The absence of side effects and lack of development of tolerance in long-term use are important factors in the decision to embark upon a trial of l-tryptophan treatment. In addition, l-tryptophan administration is not associated with impairment of visuomotor, cognitive, or memory performance nor does it elevate threshold for arousal from sleep.

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